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Management of adverse events associated with tyrosine kinase inhibitors: Improving outcomes for patients with hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. Sorafenib, regorafenib, lenvatinib and cabozantinib are tyrosine kinase inhibitors (TKIs) that target, in part, vascular endothelial growth factor receptors, and are approved in various regions of the world for the treatment of advanced HCC. All these agents are associated with a range of adverse events (AEs) that can have a substantial impact on patients' health-related quality of life. Fatigue, diarrhoea, hand–foot skin reaction, nausea, vomiting, decreased appetite, hypertension and weight loss are among the most common AEs experienced with these four TKIs. In this review, we discuss strategies for the management of these AEs in patients with advanced HCC, with the aim of maximizing treatment benefits and minimizing the need for TKI treatment discontinuation. We also consider potential TKI–drug interactions and discuss the use of TKIs in patients with liver dysfunction or who have experienced tumour recurrence after liver transplantation. Use of appropriate AE management strategies and avoidance of contraindicated drugs should help patients with advanced HCC to achieve optimal outcomes with TKIs.

Introduction

Tyrosine kinase inhibitors (TKIs) that target pro-angiogenic molecules, such as vascular endothelial growth factor receptors (VEGFRs), in the tumour microenvironment induce apoptosis by inhibiting tumour cell proliferation and angiogenesis [1]. TKIs are effective in treating a range of tumour types, including advanced hepatocellular carcinoma (HCC) [2–5]. HCC accounts for the majority of cases of primary liver cancer, which is the sixth most common cancer and the fourth most common cause of cancer-related death worldwide [6]. This is in part due to the fact that many patients with HCC have advanced disease at the time of diagnosis [7,8]. In 2007 sorafenib was the first VEGFR TKI to be approved in advanced HCC; before this there were no approved systemic therapies for advanced HCC, and the prognosis was poor [9]. The first phase 3 trial of sorafenib versus placebo in advanced HCC demonstrated a significant, yet moderate improvement in median overall survival (OS; 10.7 vs. 7.9 months, respectively; hazard ratio [HR], 0.69; 95% confidence interval, 0.55–0.87; $p < 0.001$) [2]. A further phase 3 trial showed a similar benefit of sorafenib over placebo in Asian patients with advanced HCC [10].

In 2016, a phase 3 trial investigated the efficacy of regorafenib versus placebo in patients with advanced HCC who had progressed on sorafenib. These data demonstrated that regorafenib moderately improved median OS (10.6 months vs. 7.8 months; HR, 0.63; 95% CI: 0.50–0.79; $p < 0.0001$) and progression-free survival (PFS; 3.1 months vs. 1.5 months; HR, 0.46; 95% CI: 0.37–0.56; $p < 0.0001$) compared with placebo [3]. Regorafenib was subsequently approved in 2017 for the treatment of advanced HCC following sorafenib failure.

When well tolerated, treatment with sorafenib followed by regorafenib (at radiologic progression on sorafenib) can result in a median OS of 26 months [11]. However, when this sequence is not possible due to lack of efficacy or intolerance to these drugs, the prognosis remains poor. This has led to the investigation of further treatment options. Two further anti-angiogenic TKIs, lenvatinib and cabozantinib, have recently shown benefit in advanced HCC. A phase 3 trial of lenvatinib demonstrated non-inferiority to sorafenib in the first-line treatment of advanced HCC [4], with a median OS of 13.6 months vs. 12.3 months, respectively (HR, 0.92; 95% CI: 0.79–1.06). Based on these data, lenvatinib was approved in Japan, Europe and the USA as a first-line treatment. Cabozantinib, which in addition to inhibiting VEGFR 1, 2 and 3 also inhibits c-MET and AXL, was evaluated in a phase 3 study versus placebo in patients who had received up to two prior systemic therapies, including sorafenib, and whose disease had progressed following at least one prior treatment. Cabozantinib demonstrated

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significant improvements versus placebo in median OS (10.2 months vs. 8.0 months, respectively; HR, 0.76; 95% CI: 0.63–0.92; $p = 0.005$), PFS (5.2 months vs. 1.9 months, respectively; HR, 0.44; 95% CI: 0.36–0.52; $p < 0.001$) and objective response rate (ORR; 4% vs. < 1%, respectively; $p = 0.009$) [5]. Based on these data, cabozantinib was approved in Europe and the USA for the second-line treatment of advanced HCC.

All TKIs such as sorafenib, regorafenib, lenvatinib and cabozantinib are associated with various adverse events (AEs) that can negatively impact a patient's health-related quality of life. Effective AE prevention and management are therefore important to maximize treatment benefits. Here, we review the tolerability profiles of TKIs used to treat advanced HCC, with a focus on AE management strategies. We also discuss the implications of comorbidities and drug–drug interactions for TKI tolerability in this patient population.

Methods

We identified AEs associated with sorafenib, regorafenib, lenvatinib or cabozantinib treatment of patients with advanced HCC from the initial phase 3 clinical trials for these agents. AE management strategies were identified by searching PubMed in May 2018 for English-language articles, with no date restrictions, using the following terms:

("adverse events"[title/abstract] OR "side effects"[title/abstract] OR safety[title/abstract] OR tolerability[title/abstract] OR toxicity[title/abstract]) AND (sorafenib OR regorafenib OR lenvatinib OR cabozantinib) AND (carcinoma[title/abstract] OR cancer[title/abstract]) AND (management[title/abstract] OR manage[title/abstract]).

Search results were screened manually to identify relevant articles. Owing to the wealth of sorafenib literature, only articles about sorafenib AE management in HCC were included. For regorafenib, lenvatinib and cabozantinib, articles about AE management in any solid tumours were included. Reference lists from these articles were reviewed for other potentially relevant publications. TKI–drug interaction information was identified from product labels and a literature search.

Search results

In total, 281 articles were identified and evaluated for relevance, and 30 were included in this review. An additional 16 articles that were cited in the search results were also included.

Summary of AEs associated with TKI treatment of advanced HCC

In the four seminal phase 3 trials of sorafenib, regorafenib, lenvatinib and cabozantinib, most patients experienced drug-related AEs (Table 1) [2–5]. The incidence of grade ≥ 3 AEs ranged from 45 to 75%. The most common AEs were generally similar for all four agents, and included fatigue, diarrhoea, hand–foot skin reaction (HFSR), nausea, vomiting, decreased appetite, hypertension and weight loss.

In each of these studies, a large proportion of patients experienced either an AE-related dose reduction or interruption. With sorafenib, AEs led to dose reductions in 26% of patients and dose interruptions in 44%, compared with 7% and 30% of placebo-treated patients, respectively [2]. AE-related dose reductions or interruptions were reported in 68% of patients treated with regorafenib (vs. 31% with placebo) and 62% of patients treated with cabozantinib (vs. 13% with placebo) [3,5]. The trial evaluating lenvatinib versus sorafenib as first-line treatment only reported dose reductions and interruptions owing to treatment-related AEs; these occurred in 37% and 40% of lenvatinib-treated patients, and 38% and 32% of sorafenib-treated patients, respectively [4].

The most common AEs leading to sorafenib dose reductions in the original phase 3 trial were diarrhoea (8%), HFSR (5%) and rash or desquamation (3%) [2]. HFSR (22%) and diarrhoea (10%) were also the most common AEs leading to cabozantinib dose reductions, along

Table 1
Common adverse events in phase 3 trials of tyrosine kinase inhibitors in advanced hepatocellular carcinoma.

Trial details	Adverse events occurring in ≥15% of patients	Incidence of grade ≥3 adverse events[a,b] (%)
Sorafenib:	Any	45
NCT00105443	Diarrhoea	10–11
(*N* = 602) [2]	Fatigue	10
Sorafenib 400 mg twice daily	Abdominal pain	9
	Weight loss	2
	Decreased appetite	3
	Nausea	1
	Ascites	6–7
	HFSR	8
	Rash/desquamation	1
	Oedema, limb	3
	Vomiting	2
Regorafenib:	Any	66
NCT01774344	HFSR	13
(*N* = 573) [3]	Diarrhoea	3
Regorafenib 160 mg daily during weeks 1–3 of each 4-week cycle	Fatigue	9
	Hypertension	15
	Decreased appetite	3
	Increased blood bilirubin	11
	Abdominal pain	3
	Increased AST	11
	Nausea	1
	Constipation	< 1
	Ascites	4
	Anaemia	5
	Limb oedema	1
	Increased ALT	4
	Hypoalbuminaemia	2
Lenvatinib:	Any	75
NCT01761266	Hypertension	23
(*N* = 954) [4]	Diarrhoea	4
Lenvatinib 12 mg daily for bodyweight ≥60 kg or 8 mg daily for bodyweight < 60 kg	Decreased appetite	5
	Weight loss	8
	Fatigue	4
	HFSR	3
	Proteinuria	6
	Dysphonia	< 1
	Nausea	1
	Decreased platelet count	5
	Abdominal pain	2
	Vomiting	1
	Constipation	1
	Increased blood bilirubin	7
Cabozantinib:	Any	68
NCT01908426	Diarrhoea	10
(*N* = 707) [5]	Decreased appetite	6
Cabozantinib 60 mg daily	HFSR	17
	Fatigue	10
	Nausea	2
	Hypertension	16
	Vomiting	< 1
	Increased AST	12
	Asthenia	7
	Dysphonia	1
	Constipation	< 1
	Abdominal pain	2
	Weight loss	1
	Increased ALT	5

ALT: alanine aminotransferase; AST: aspartate transaminase; HFSR: hand–foot skin reaction.

[a] Adverse event grading from different versions of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) were used for sorafenib (version 3.0), regorafenib (version 4.03), lenvatinib (version 4.0) and cabozantinib (version 4.0).

[b] Incidences of grade ≥3 adverse events for sorafenib, regorafenib and cabozantinib were calculated by summing grade 3 and grade 4 events.

Table 2
A general algorithm for dose interruptions and reductions according to the severity of tyrosine kinase inhibitor-associated adverse events.

Grade or severity of AE	Treatment	Modification of dose
Grade 0, 1 (mild) or 2 (moderate)	Unchanged	No modification
Grade 3 (severe)	Interruption until recovery to < grade 2	First episode: try to restart at full dose Second episode: reduce the dose until the AE has reduced in severity by 1 grade
Grade 3–4	As there is a risk of death, consider a permanent reduction or interruption	

AE: adverse event.

with fatigue (7%), hypertension (7%) and increased aspartate transaminase levels (6%) [5]. AEs leading to dose reductions and interruptions were not reported for regorafenib or lenvatinib [3,4]. In addition to AE-related dose reductions or interruptions, a smaller but substantial proportion of patients discontinued treatment and withdrew from each study due to AEs. Discontinuations owing to treatment-related AEs occurred in similar proportions of patients treated with sorafenib (11%), regorafenib (10%), lenvatinib (9%) and cabozantinib (16%) [2–5]. AE management and minimization may improve patients' quality of life and reduce treatment discontinuation.

To ensure that treatment efficacy is optimal, maintaining the dose intensity recommended on each TKI's label is of major interest. Dose reductions or treatment interruptions should be considered on a case-by-case basis according to the severity and nature of each AE. Given that such strategies are specific to each TKI, a general algorithm for TKI-associated AE management is provided in Table 2.

Association of TKI AEs with positive treatment outcomes

Some TKI-associated AEs correlate with improved patient outcomes; sorafenib-related dermatological AEs are associated with improved survival [12–17]. A prospective study in 147 sorafenib-treated patients with advanced HCC demonstrated that those who experienced dermatological AEs within the first 60 days of treatment had significantly increased time to progression (8.1 months vs. 3.9 months; $p = 0.016$) and OS (18.2 months vs. 10.1 months; $p = 0.009$), compared with those who did not [14]. A retrospective, bivariate analysis of patients enrolled in the phase 3 study of regorafenib showed that HFSR is also associated with better outcomes for regorafenib-treated patients [18].

TKI-related diarrhoea and hypertension have also been associated with positive outcomes in advanced HCC [12,13,19,20]. An observational study of patients who experienced diarrhoea or hypertension after sorafenib treatment showed significant improvements in OS compared with those who did not (median OS: diarrhoea, 14 months vs. 7 months; hypertension, 13 months vs. 8 months; for patients with and without each AE, respectively) [13]. Although the association between AEs and outcomes in advanced HCC has not been assessed for lenvatinib, median OS for patients with differentiated thyroid cancer treated with lenvatinib was significantly longer for patients who experienced grade ≥ 2 hypertension than for those who did not (not reached vs. 21.7 months) [21]. Currently, there are no data available on any associations between AEs and outcomes of cabozantinib treatment in any tumour type.

Occurrence of HFSR, diarrhoea and hypertension are all likely to be related to the mechanism of action of TKIs. Inhibition of platelet-derived growth factor receptors (PDGFRs) and c-Kit in the eccrine glands of the dermis and epidermis of the palms and soles may contribute to HFSR [22,23]. A decrease in peripheral blood flow following sorafenib treatment has also been linked to the emergence of this AE [24]. Hypertension may result from TKI inhibition of vascular endothelial growth factor (VEGF)-mediated nitric oxide synthase upregulation, thereby inhibiting vasomotor function and promoting degeneration of small blood vessels [25]. VEGF and VEGFRs are also expressed in intestinal endothelial cells, and c-Kit is important for the function of interstitial cells of Cajal in the gastrointestinal tract [26,27]. Consequently, it has been suggested that VEGFR and c-Kit inhibition may cause diarrhoea [28]. Management of HFSR, diarrhoea and hypertension is especially important; although they are associated with positive treatment outcomes, they are among the most frequently experienced AEs [2–5]. Furthermore, if TKI tolerability can be improved, patients are more likely to remain on treatment and therefore experience better outcomes [29,30].

Management of AEs associated with TKI therapy

Over the last decade, a wealth of strategies have been developed for the management of sorafenib-associated AEs. Most of these strategies can be used in the management of AEs associated with other TKIs. Moreover, many AEs associated with regorafenib, lenvatinib and cabozantinib in the treatment of advanced HCC are consistent with AEs observed in the treatment of other solid tumours [31–35]. Consequently, where information is lacking for managing AEs observed in the treatment of advanced HCC, AE management approaches that are established for other tumour types can be considered here. Management recommendations for the most common TKI-associated AEs are discussed below and summarized in Table 3.

Hand–foot skin reaction

TKI-associated HFSR (also known as palmar–plantar erythrodysesthesia or hand–foot syndrome) generally affects the palms of the hands and soles of the feet. Occasionally, symptoms may also occur on other areas such as the knees and elbows. HFSR of any grade was the most common AE associated with regorafenib in the phase 3 advanced HCC study, occurring in 53% of patients (Table 1) [3]. It was also among the most common AEs in the sorafenib, lenvatinib and cabozantinib phase 3 advanced HCC studies (occurring in 21%, 27% and 46% of patients, respectively) [2,4,5]. Grade 3 HFSR, which can substantially impair patients' ability to perform daily tasks and overall quality of life, occurred in 3–17% of patients in these studies (Table 1) [2–5].

Many recommendations for managing HFSR are based on clinical experience rather than scientific evidence. For patients with advanced HCC, most recommendations are based on experience with sorafenib; however, these are consistent with recommendations made for regorafenib, cabozantinib and lenvatinib in other tumour types (Table 3). Before starting TKI treatment, it is important to educate patients about the symptoms of HFSR, and to take steps to soften and remove any existing areas of hyperkeratosis or callused skin on patients' hands and feet [36–42]. Patients should be regularly monitored to proactively manage any occurrence of skin toxicities once TKI treatment has started, especially at the start of therapy (e.g. every few weeks for the first 2–4 months) [36,37,42–44]. To minimize the development of calluses and hyperkeratosis, patients should use emollients regularly [36,39,41,42,45–49]. In sorafenib-treated patients with advanced HCC, prophylactic emollients containing 10% urea, used three times a day, have been shown to reduce the incidence and delay the onset of HFSR [48]. Minimizing unnecessary friction can be achieved by wearing cotton socks and gloves, padded insoles and well-fitting shoes [37,39,41,42,46,47,50] and avoiding heavy lifting [46]. Other

Table 3
Management of common adverse events associated with tyrosine kinase inhibitors for advanced hepatocellular carcinoma.

Adverse event	Recommended management strategies
HFSR	**Prophylactic management:** ● Existing areas of hyperkeratosis or callused skin should be softened and removed before TKI initiation ● Emollients containing 10% urea should be used three times daily ● Hot water should be avoided ● Non-fragranced, non-foaming skin products should be used, hand sanitizers containing alcohol should be avoided; hands should be completely dried after washing ● Sun exposure and unprotected cold exposure should be avoided ● Friction may be minimized using cotton socks and gloves, padded insoles and well-fitting shoes, and by avoiding heavy lifting **AE management:** ● Preventative measures should be continued ● Use emollients containing 20–40% urea ● Moisturizers containing salicylic acid, ammonium lactate or alpha hydroxyl acid may be used to soften and exfoliate hyperkeratotic and callused areas ● Cooling hand and foot baths containing magnesium sulphate may reduce pain and soften calluses ● For grade 2/3 HFSR, consider using topical treatments such as cortisone and 0.05% clobetasol ● If topical treatments are ineffective, consider using oral analgesia such as pregabalin and opioids (use with caution) ● To prevent infection, cracked skin may be soaked in equal parts vinegar and water for 10 min each day ● In severe cases it may be necessary for a trained professional to drain blisters and remove areas of hyperkeratosis
Diarrhoea	**Prophylactic management:** ● Using a stool diary to help identify foods that may trigger digestive problems may be useful **AE management:** ● Caffeine, alcohol, spicy or fatty foods, dairy products and foods high in insoluble fibre should be avoided ● Consumption of bananas, rice, potatoes, apple sauce, toast and probiotics may be helpful ● Concomitant lactulose dose reduction may be necessary ● Fluid intake should be increased, and electrolytes should be monitored and replaced when necessary ● In cases that cannot be managed by dietary changes, loperamide (4 mg then 2 mg every 4 h, or after each loose stool until the desired effect is achieved) may be prescribed. For patients who frequently experience diarrhoea, loperamide may also be taken pre-emptively, 30 min before TKI treatment ● Loperamide-refractory diarrhoea may be treated with atropine-diphenoxylate, codeine or tincture of opium, if appropriate
Fatigue	**AE management:** ● Rest periods should be incorporated into the patient's daily schedule ● For patients who are fit enough, daily exercise such as walking, or weight-bearing exercises may be useful ● A nutritious diet and proper hydration should be encouraged ● The presence of underlying conditions including hypothyroidism, low testosterone in men (via an endocrinology consultation), pain, sleep dysfunction, emotional distress, depression and anaemia should be evaluated and treated as required. However, care should be taken with the administration of testosterone, due to the potential hormone-sensitivity of HCC cells. ● Treatment of other adverse events such as diarrhoea, vomiting, nausea and weight loss may reduce fatigue ● Psychostimulants such as caffeine, or methylphenidate or modafinil for more severe cases, may be considered; however, care should be taken when prescribing modafinil owing to potential interactions with TKIs ● TKI dosing in the evening rather than the morning may reduce daytime fatigue
Nausea and vomiting	**AE management:** ● Chocolate, caffeine, alcohol and nicotine should be avoided ● Pharmacological treatment with metoclopramide or levosulpiride may be considered ● Ondansetron and granisetron should be used with caution owing to potential interactions with TKIs
Decreased appetite and weight loss	**Prophylactic management:** ● Appetite and weight should be monitored in each treatment cycle ● A nutritious diet should be encouraged **AE management:** ● Appetite stimulants such as dronabinol or megestrol acetate should be considered ● Any underlying nausea should be treated ● A high-calorie diet and dietary supplements should be recommended
Hypertension	**Prophylactic management:** ● Blood pressure should be controlled before initiating TKI treatment ● Blood pressure should be monitored regularly for the first few months of treatment **AE management:** ● Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or beta blockers should be used to treat hypertension ● Calcium channel blockers may be considered, but careful selection is necessary to avoid interactions with TKIs ● Caution should be taken when using thiazide diuretics owing to the risk of diarrhoea

AE: adverse event; HFSR: hand–foot skin reaction; NSAIDs: non-steroidal anti-inflammatory drugs; TKI: tyrosine kinase inhibitor.

preventative strategies include avoiding hot water [41–43,51] and hand sanitizers containing alcohol [42], using non-fragranced, non-foaming skin cleansers [42,46,47], ensuring that hands are dried completely after washing, and avoiding sun exposure and unprotected exposure to cold [51].

Once HFSR develops, preventative measures should be continued. Emollients containing 20–40% urea may be used, and additional topical treatments should be considered [50,52]. Moisturizers containing salicylic acid, ammonium lactate or alpha hydroxyl acid may be useful to soften and exfoliate hyperkeratotic and callused areas [36,37,39–41,45,50]. Cooling hand and foot baths containing magnesium sulphate are also suggested to reduce pain and soften calluses, making them easier to remove [37,40,43,47,51]. Topical cortisone, corticosteroids such as 0.05% clobetasol, and topical analgesia that includes lidocaine are commonly recommended for symptomatic relief of grade 2/3 HFSR [38,39,42,43]. If these are not effective, oral analgesics including non-steroidal anti-inflammatory drugs (NSAIDs), pregabalin and opioids may be considered with caution [36,44,52,53].

To prevent infection of cracked and painful skin, patients may be advised to soak the affected area in a solution of equal parts vinegar and water for 10 min twice a day [41]. In cases where severe hyperkeratosis and blistering occur, a trained professional should drain the blisters and remove areas of hyperkeratosis using sterile instruments; antibiotics should be used when infection occurs [41,46]. When severe HFSR does not adequately respond to the methods described above, TKI dose interruptions or reductions should be considered [36,37,39–41,45]. Once severity decreases to grade 1, the full dose can be resumed; however, if this results in worsening of the HFSR, a permanent lower dose may be an option [45,50,52]. Discontinuation of TKI therapy should be considered only in the most severe or recurrent cases of HFSR [37,40,44,51].

Diarrhoea

Diarrhoea was the most common AE associated with sorafenib and cabozantinib, occurring in 55% and 54% of patients with advanced HCC, respectively (Table 1) [2,5]. It was the second most common AE reported in patients who received regorafenib and lenvatinib [3,4]; grade ≥ 3 diarrhoea occurred in 3–11% of these patients (Table 1) [2–5].

Generally, recommendations for TKI-associated diarrhoea management are consistent across tumour types (Table 3). A specific recommendation for patients with advanced HCC is to reduce any dose of concomitant lactulose [43]. Aside from this, to enable rapid reporting and management, patients should be encouraged to complete a stool diary and promptly report any concerns to their healthcare provider [45]. Diarrhoea may also be managed by making dietary changes, including avoiding caffeine, alcohol, spicy or fatty foods, dairy products and foods high in insoluble fibre [36,37,42,43,45,50,54]. Use of a food diary may be helpful for identifying particular items that exacerbate diarrhoea [51]. Additionally, consumption of bananas, rice, potatoes, apple sauce, toast and probiotics may help to alleviate symptoms [28,53]. It is important to ensure that patients with diarrhoea do not become dehydrated; fluid intake should be increased, and electrolytes monitored and replaced when necessary [36,40,43,45,47].

If diarrhoea cannot be managed by dietary changes, pharmacological intervention may be necessary. Loperamide is widely recommended; an initial dose of 4 mg should be followed by 2 mg every 4 h, or after each loose stool until symptoms subside [44,45,47,50,54]. For patients who frequently experience diarrhoea, loperamide may be taken as a pre-emptive measure 30 min before each TKI dose [43–45,51]. When diarrhoea is not controlled by loperamide, other medications such as atropine-diphenoxylate, octreotide, codeine or tincture of opium may be considered [36,37,40,44,50]. Cholestyramine should not be taken in combination with any other anti-diarrhoea medications because of the potential for drug–drug interactions [43,51]. When severe or persistent diarrhoea is unresponsive to management, TKI dose interruptions or reductions should be considered; if tolerated, the full dose can be resumed once symptoms resolve [36,39,41,43,45,49]. Some patients may need to be screened for exocrine pancreatic insufficiency, which can be treated with pancreatic enzyme replacement [55].

Fatigue

Fatigue may develop as a side effect of TKI treatment or may be a symptom of advanced HCC. In phase 3 studies, fatigue occurred in 46% of patients who received sorafenib, 40% of patients who received regorafenib, 30% of patients who received lenvatinib and 45% of those who received cabozantinib (Table 1) [2–5]. Grade ≥ 3 fatigue occurred at rates of 4–10% in these patients (Table 1).

To encourage early reporting and management to prevent worsening, it is important to educate patients about the possibility of developing treatment-related fatigue (Table 3) [42,44,53]. Patients who experience fatigue should be advised to incorporate rest periods into their daily schedule [42,45,47]. For patients with colorectal cancer, there is evidence to suggest that physical exercise improves fatigue [56]. Although many patients with advanced HCC are not well enough to exercise strenuously, daily activity, such as walking or weightbearing exercises, should be encouraged for those who are able [41–43,45,47,49]. It is also important to ensure that patients are properly nourished and hydrated [36,40,45,49].

Fatigue may also be a consequence of malnutrition caused by other TKI-associated AEs, including diarrhoea, vomiting and nausea; management of these AEs as described in this review may alleviate fatigue. Patients with fatigue should also be assessed and treated for hypothyroidism, which is commonly associated with TKI treatments [36,37,41,43,45]. Other potential underlying causes of fatigue, such as low testosterone in men, pain, sleep dysfunction, emotional distress, depression and anaemia, should also be considered and treated as required [28,37,45,47,49]. Psychostimulants may be considered for treatment of TKI-related fatigue [45,49,50,53]. In particular, methylphenidate and modafinil have shown efficacy in patients with severe cancer-related fatigue [57,58]; however, care should be taken when using modafinil owing to the risk of interaction with TKIs through CYP3A4 (Table 4) [59].

Caffeine could be incorporated into the diet if diarrhoea or nausea and vomiting are not an issue [43,53]. Patient diaries can be useful to determine whether fatigue is cancer-related or treatment-related and may inform dose modifications [47]. To reduce daytime fatigue, patients may find it helpful to take TKIs in the evening [43]. In most cases, dose reductions or interruptions should only be considered for grade ≥ 3 fatigue (which is a major, limiting AE, not resolvable with rest), and the full dose should be resumed once fatigue is resolved [36,42,45].

Nausea and vomiting

In the phase 3 clinical trials discussed here, nausea rates were 24% for sorafenib, 17% for regorafenib, 20% for lenvatinib and 31% for cabozantinib (Table 1) [2–5]. Vomiting occurred in 15%, 13%, 16% and 26% of patients, respectively. In each study, ≤ 2% of patients who received the investigational drug experienced nausea or vomiting at grade ≥ 3 (Table 1).

There is a lack of evidence-based management strategies for TKI-related nausea and vomiting. It has been suggested that avoiding chocolate, caffeine, alcohol and nicotine may be useful (Table 3) [53]. Antiemetics such as metoclopramide, levosulpiride or ondansetron may alleviate symptoms. Ondansetron should be used with caution, as it may cause QT prolongation, which is also an AE that can arise with sorafenib, cabozantinib and lenvatinib therapy [49,60–64]. Based on limited clinical experience from one centre, other pharmacological treatments that may be useful include the analgesic fentanyl and the anti-diarrhoea agent racecadotril [63].

Decreased appetite and weight loss

Decreased appetite occurred in 29% of patients who received sorafenib, 31% of patients who received regorafenib, 34% of patients who received lenvatinib and 48% of those who received cabozantinib (Table 1) [2–5]. Weight loss was experienced by 14–31% of these patients (Table 1) [2–5].

Management recommendations for decreased appetite and weight loss across TKIs and tumour types include monitoring the patient's appetite and weight in each treatment cycle and encouraging a nutritious diet (Table 3) [36,53]. For patients who experience decreased appetite, stimulants such as dronabinol or megestrol acetate may be administered [36,44]. Caution should be taken when treating patients with advanced HCC with megestrol acetate, because there is a risk of venous thrombosis [65]. Treatment of nausea as described above may

Table 4
Examples of CYP3A modulators and P-glycoprotein substrates and modulators.

CYP3A modulators				
Drug class	Strong inhibitors[a]	Moderate inhibitors[a]	Strong inducers[b]	Moderate inducers[b]
Other	Grapefruit juice, grapefruit, carambola (star fruit), Seville oranges, conivaptan,	–	St. John's wort	–
Antifungal agents	Itraconazole, ketoconazole, posaconazole, voriconazole	Clotrimazole, fluconazole	–	–
Antibiotics	Troleandomycin, clarithromycin	Ciprofloxacin, erythromycin	Rifampicin	–
Cardiovascular agents	Diltiazem	Dronedarone, verapamil	–	Bosentan
Immunosuppressants	–	Cyclosporine	–	–
HIV therapies	Cobicistat, indinavir, ritonavir, nelfinavir	–	–	Efavirenz, etravirine
Hepatitis C therapies	Boceprevir, telaprevir	–	–	–
Gastric agents	–	Aprepitant, cimetidine	–	–
Anticonvulsants and other neurologic agents	Nefazodone	Fluvoxamine, tofisopam	Carbamazepine, phenytoin	Modafinil

P-glycoprotein substrates and modulators			
Drug class	Substrates[c]	Inhibitors[d]	Inducers[e]
Other	–	Grapefruit juice, grapefruit, carambola (star fruit), Seville oranges	St. John's wort
Antifungal agents	–	Itraconazole	–
Antibiotics	–	Clarithromycin	Rifampicin
Anticoagulants	Dabigatran	–	–
Antihistamines	Fexofenadine	–	–
Cardiovascular agents	Digoxin	Amiodarone, carvedilol, dronedarone, propafenone, quinidine, verapamil, ranolazine	–
Immunosuppressants	–	–	Cyclosporine, dexamethasone
HIV therapies	–	Lopinavir, ritonavir, saquinavir, tipranavir	Tipranavir
Hepatitis C therapies	–	Telaprevir	–
Anticonvulsants and other neurologic agents	–	–	Carbamazepine, phenytoin, venlafaxine

Examples from US FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [59] and Wessler JD *et al.* 2013 [75].
AUC: area under the curve; FDA, Food and Drug Administration.
[a] Drugs that increase the AUC of sensitive index substrates of CYP3A by ≥5-fold (strong) or ≥2 to < 5-fold (moderate) [59].
[b] Drugs that decrease the AUC of sensitive index substrates of CYP3A by ≥80% (strong) or ≥50% to < 80% (moderate) [59].
[c] Drugs that have AUC increased by ≥2-fold with verapamil or quinidine co-administration and that undergo *in vitro* transport by P-glycoprotein expression systems, but that are not extensively metabolized [59].
[d] Drugs that increase the AUC of digoxin by ≥2-fold with co-administration and that inhibit P-glycoprotein *in vitro* [59].
[e] Drugs that decrease the AUC of digoxin or fexofenadine by > 0.2-fold [82].

also improve appetite [28]. Some patients may experience asthenia–anorexia–cachexia syndrome, characterized by weight loss, weakness and fatigue. This condition can be treated with corticosteroids, although these may only be effective in the short term [36,66]. Patients who experience weight loss should be assessed for tumour progression and encouraged to consume a high-calorie diet and take dietary supplements [36,53]. In severe cases, if treatment-related, TKI dose reductions may be considered [36].

Hypertension

Hypertension was the most common AE experienced by patients treated with lenvatinib, with any grade hypertension occurring in 42% of patients and grade ≥ 3 hypertension occurring in 23% of patients (Table 1) [4]. Hypertension was also common in patients treated with regorafenib (any grade, 31%; grade ≥ 3, 15%) and those treated with cabozantinib (any grade, 29%; grade ≥ 3, 16%; Table 1) [3,5]. The overall proportion of patients who experienced hypertension while receiving sorafenib was not reported because it was below 10%; however, sorafenib-related any grade and grade ≥ 3 hypertension were reported in 5% and 2% of patients, respectively [2]. It should be noted that National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3 was used for the phase 3 trial of sorafenib, whereas version 4 was used for the other trials discussed here [67,68]. Between these versions, the grading of hypertension was significantly modified, leading to more patients being classified as having hypertension when NCI CTCAE version 4 was used.

Recommendations for the management of hypertension in a range of tumour types are generally consistent for the four TKIs discussed here (Table 3). Blood pressure should be controlled before TKI treatment is initiated; it should then be monitored regularly for the first few months [21,39,40,42,43,45]. Monitoring can be conducted at clinic visits, and if appropriate, patients may self-monitor at home multiple times per week [40,42,43]. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and beta blockers are suitable for patients who develop hypertension while receiving TKIs [39,40,42,43,45,49]. Calcium channel blockers (CCBs) are also suitable [40,42,43,49]; however, caution should be taken when choosing which agent to use. Diltiazem and verapamil are non-dihydropyridine CCBs that inhibit CYP3A4; these and similar agents should be avoided with regorafenib and cabozantinib owing to potential drug–drug interactions (Table 4) [28,53,69]. There is also evidence that the dihydropyridine CCB nifedipine may increase VEGF secretion [70], which is undesirable, as it may counteract the effects of TKI treatment. Other dihydropyridine CCBs that do not interact with this pathway should therefore be considered. Thiazide diuretics are also an option [40,44,53], although they may increase the risk of patients experiencing diarrhoea [42]. A combinatorial treatment approach may be required to manage hypertension in some cases, although ACE inhibitors and ARBs should not be combined [71]. When antihypertensives are not effective, TKI dose reductions or interruptions may be necessary [21,38,45,51]. In persistent cases, TKI discontinuation should be considered [38,45,51].

Impact of concomitant medications and comorbidities on TKI AEs in advanced HCC

CYP3A4 modulators

Sorafenib, regorafenib, lenvatinib and cabozantinib are all metabolized by the liver enzyme CYP3A4 [60,61,64,72]; as such, concomitant use of drugs that modulate activity of CYP3A4 can affect tolerability. Pharmacokinetic evaluation showed that administration of the antifungal ketoconazole, a strong CYP3A4 inhibitor, increased plasma exposure of regorafenib and cabozantinib by approximately 33% and 38%, respectively [60,72], although ketoconazole had no clinically relevant effect on sorafenib or lenvatinib pharmacokinetics [64,73]. Based on these findings, strong CYP3A4 inhibitors should be avoided with regorafenib and cabozantinib but may be used with sorafenib and lenvatinib [60,64,72,73]. Commonly used CYP3A4 inhibitors include certain antibiotics, antifungal agents, immunosuppressants and grapefruit juice (Table 4).

Inducers of CYP3A4 activity have the potential to increase TKI metabolism and decrease efficacy. Pharmacokinetic evaluation found that administration of the antibiotic rifampicin, a strong CYP3A4 inducer, led to substantial reductions in plasma exposure of sorafenib (by 37%), regorafenib (50%) and cabozantinib (77%) [60,64,72]; however, a smaller, non-clinically relevant reduction in plasma exposure was seen for lenvatinib (18%) [74]. Commonly used CYP3A4 inducers include the anti-epileptic carbamazepine, modafinil and the herbal supplement St John's wort (Table 4). It is recommended that these agents are avoided with sorafenib, regorafenib and cabozantinib; however, they may be used with lenvatinib.

P-glycoprotein modulators and substrates

Sorafenib and cabozantinib inhibit the transport protein P-glycoprotein (P-gp), and therefore a build-up of P-gp substrates may occur following their administration [60,64]. P-gp substrates, such as the antihistamine fexofenadine, should therefore be administered with caution in patients receiving sorafenib or cabozantinib (Table 4) [60,64,75]. Two active metabolites of regorafenib are P-gp substrates [72]; therefore, concomitant use of P-gp inhibitors or inducers may affect the efficacy and tolerability of regorafenib and should be avoided. A study of 15 healthy adults receiving lenvatinib showed that P-gp inhibition occurred following a single dose of rifampicin, leading to a non-clinically meaningful increase in lenvatinib plasma exposure [74]. No data are available to exclude lenvatinib as an inducer of P-gp; therefore, P-gp substrates should be administered with caution in patients receiving lenvatinib [61]. Commonly used substrates, inducers and inhibitors of P-gp are shown in Table 4.

Gastroprotectants

Proton-pump inhibitors (PPIs) that are commonly used to treat reflux and gastric ulcers work by reducing the amount of acid produced by the stomach thus increasing the pH. There is evidence to suggest that increased stomach pH may impair the acid-dependent absorption of some TKIs. In a phase 2 study of sorafenib plus erlotinib, sorafenib plasma concentration was reduced in patients who were taking concomitant PPIs [76]. Cabozantinib absorption is also acid-dependent; however, concomitant use of the PPI esomeprazole had no effect on cabozantinib plasma exposure [77]. There are no data regarding the effects of PPIs on absorption of regorafenib or lenvatinib. It is therefore suggested that PPIs should be avoided with sorafenib and used with caution in patients treated with regorafenib or lenvatinib. Overall, there is widespread use of PPIs in patients receiving oral TKIs; however, owing to potential negative effects on TKI absorption, they should be used with care.

Liver dysfunction

Patients with advanced HCC often have reduced liver function (Child–Pugh class B or C) resulting in impaired drug metabolism and reduced albumin production. This reduced metabolism can increase the plasma concentration of TKIs that remain unbound to albumin [78,79], which may reduce TKI tolerability. The phase 3 studies discussed here were conducted in patients with relatively good liver function (Child–Pugh A) at screening. A phase 4 study of sorafenib treatment in HCC found no difference in the incidence of drug-related AEs between patients with Child–Pugh A and Child–Pugh B liver function. However, rates of serious AEs and AE-related treatment discontinuation were higher in patients with Child–Pugh B versus A liver function [80]. These findings suggest that implementation of the AE management strategies described in this article may be of particular importance to minimize AE severity and AE-related discontinuation in patients with reduced liver function. Further studies are required to characterize the efficacy and tolerability of regorafenib, lenvatinib and cabozantinib in patients with liver impairment.

Genetic variation in CYP3A4 liver enzyme function may also affect the metabolism of TKIs [81], and may therefore alter their tolerability. Over 40 CYP3A4 genetic variants have been identified, of which at least 14 alter CYP3A4 enzyme levels or activity [81]. Genetic screening for these mutations is not routine in many centres. However, in cases of severe unmanageable toxicity, the presence of functional variants of these enzymes should be considered, even if this is not easily assessible in clinical practice. Alternatively, levels of sorafenib in plasma may be measured using high-performance liquid chromatography/electrospray ionization tandem mass spectrometry, which has the potential to be useful for identifying patients with unusually high plasma drug concentrations [82]. Using this technique, the TKI dose could be modified to achieve the appropriate plasma drug concentration, although this approach has not yet been prospectively evaluated.

Tumour recurrence after liver transplantation

Patients who have undergone liver transplantation to treat HCC may experience tumour recurrence. These patients may be suitable for systemic TKI therapy; however, they were also excluded from the phase 3 trials discussed here [2–5], and therefore no robust data exist regarding TKI efficacy and safety in this population. A 2015 systematic review of case reports and small retrospective studies found that patients with recurrent HCC after liver transplantation who were treated with sorafenib (n = 76) experienced improved survival, compared with those who received best supportive care (n = 54; weighted mean [83]: 12.1 [9.95] months vs. 3.3 [2.12] months, respectively) [82,84]. However, this review also highlighted that 7/23 included studies reported AEs that required dose reductions and discontinuations in a high proportion of patients. Across the 23 studies, 197 patients received sorafenib (alone or in combination with modified immunosuppressants) after liver transplantation; of these, 42.1% required dose reductions, and 9.6% discontinued treatment due to AEs [82,84].

An additional consideration when using TKIs to treat patients who have undergone liver transplantation is the requirement for long-term immunosuppression. Given that some immunosuppressants, including cyclosporine, have the potential to interact with TKIs (Table 4) [59], careful selection of compatible therapies is important; suitable examples include tacrolimus and mycophenolate mofetil. Overall, there is a need for prospective studies to characterize the efficacy and tolerability of TKIs for recurrent HCC in these patients.

Conclusions

Sorafenib, regorafenib, lenvatinib and cabozantinib have demonstrated efficacy for the treatment of advanced HCC. However, AEs are common with all these treatments, and proactive AE management is

therefore essential to optimize tolerability and patients' quality of life. As discussed here, effective management strategies include a range of pharmacological and non-pharmacological approaches. When considering pharmacological management and treatment for comorbid conditions, it is important to consider potential interactions of concomitant medications with TKIs, as there may be tolerability implications. In cases of unmanageable tolerability issues, comorbidities such as impaired liver function and genetic variations in liver enzyme function should be considered as possible underlying factors. By employing appropriate preventative and management strategies, it should be possible to mitigate many tolerability issues associated with TKI treatment. This may lead to a reduced need for TKI treatment discontinuation and contribute to better outcomes for patients with advanced HCC.

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Author contributions

All authors made substantial contributions to the conception and design of the study, drafting the article or revising it critically for important intellectual content and final approval of the version to be submitted.

Declaration of interest

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